Remarks/Arguments

Claims 49-54 and 61-75 are currently pending.

Rejections based under 35 U.S.C § 103

Claims 49-54, 61-63, 65-69 and 71-74 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,327,410 B1, filed September 11, 1998) in view of Brenner (U.S. Patent No. 5,863,722, filed June 7, 1995) and in view of the definitions of Morris ed. (Academic Press Dictionary of Science and Technology, Academic Press, 1992, page 821).

The Examiner's position appears to be that Walt teaches all elements of the rejected claims except that "they do not specifically teach at least one microsphere subpopulation does not have an optical signature." Moreover, the Examiner asserts that Brenner provides this element and that one of ordinary skill in the art would have been motivated to apply the microspheres not having an optical signature as taught by Brenner et al. and the non-optical encoding taught by Walt et al. to the microsphere compositions of Walt et al. and to provide at least one subpopulation of microsphere without an optical signature thereby eliminating the need to provide optical signatures on all the microspheres for the obvious benefits of simplicity. Applicants respectfully traverse.

Walt and Brenner have been described in prior responses. H

Claims 49 and 61 (from which all other claims depend) are directed to a method of determining the presence of a target analyte in a sample through the use of subpopulations of

microspheres randomly distributed on a surface, wherein at least one subpopulation does not contain an optical signature and the use of fiducials to register first and second data images to create registered first and second images and comparing the first and second registered data images to determine the presence or absence of the target analyte.

As the Examiner is aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Initially, Applicants note that not all claim elements are present in Walt, Brenner or the combination of the two. Namely, Applicants point to claim 49, elements b) and e). These elements recite "using said fiducial to register said first [second] data image to create a registered first [second] data image". However, Applicants note that the section of Walt referred to by the Examiner describes the use of a positional coding system that utilized sub-bundles. The location of sub-bundles within an array are identified through methods that can utilize marker beads, i.e. beads containing unique tags for each subarray. Likewise, claim 61 sets forth a method that includes "providing a registered first data image...acquiring a second data image...using said fiducial to register said second data image to create a registered second data image; and comparing said first and said second registered data images to determine the presence or absence of said target analyte."

However, the mere recitation of identifying the location of subarrays does not disclose "using said fiducial to register said first [second] data image to create a registered first [second] data image" and "comparing said first and second registered data images to determine the presence or absence of said target analyte" because the location of the subarrays in the methods of Walt et al. can be determined without the claimed step of creating a registered data image. In this regard, the Office Action does not point to any teaching or suggestion of creating a registered data image in Walt et al. taken alone or in combination with the secondary references. That is, in contrast to identifying sub-arrays, which each contain unique tags for each sub-array, the present claims recite that the array comprises a fiducial that serves to register first and second images to generate first and second registered images which are compared to determine the presence or absence of the target analyte.

Moreover, Applicants note that Brenner and Morris do not cure the deficiencies of Walt et al. because they fail to teach or suggest "using said fiducial to register said first [second] data image to create a registered first [second] data image" and "comparing said first and second registered data images to determine the presence or absence of said target analyte". Accordingly, Applicants submit that the cited references either alone or in combination fail to teach or suggest the presently claimed subject matter.

In addition, Applicants maintain that even if all of the elements of the claimed invention were taught or suggested by the combination of references, one of ordinary skill in the art would not have been motivated to combine the references. The Examiner suggests that one of skill in the art would have been motivated to combine references because it was obvious to apply the microspheres not having an optical signature of Brenner et al. and the non-encoding optical signature of Walt with the microsphere compositions of Walt et al. and to provide at least one

subpopulation of microspheres without an optical signature for simplicity. See page 3 of the Office Action.

However, Applicants submit that this is a legally incorrect determination of motivation. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F 2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). There is no suggestion in either reference of modifying or combining the references to reach the claims of the present invention.

Furthermore, the purpose of the arrays of Walt et al. is to analyze complex systems. In particular, Walt et al. teach that the compositions and methods of their invention allow fiber optic arrays, which previously could only conveniently be made to include tens of functionalities, to handle larger arrays (see, for example, column 3, lines 13-26) and upwards of a billion or more bioactive agents (see paragraph spanning columns 4 and 5). Nowhere in the cited references is there a suggestion of simplifying the system of Walt et al. by reducing the number of optically useful beads as suggested in the Office Action. Rather such a simplification would limit the real estate available on the arrays of Walt et al. by excluding beads with optical signatures from assembling on the array for use in the optical detection methods of Walt et al. This would be contrary to the advantages of the methods of Walt et al. in handling complex systems. Thus, Walt et al. teaches away from the combination suggested in the Office Action.

Accordingly, because not all claim elements are present in the cited references and because there is inadequate motivation for the combination of the references, Applicants submit that the rejection is improper. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 64, 70 and 75 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Walt et al. (U.S. Patent No. 6,327,410, filed September 11, 1998) in view of Brenner (U.S. Patent No. 5,863,722, filed June 7, 1995) and in view of the definitions of Morris ed. (Academic Press Dictionary of Science and Technology, Academic Press, 1992, page 821) as applied to claims 49 and 61 and further in view of Augenlicht (U.S. Patent No. 4,981,783, filed April 16, 1986).

Claims 64, 70 and 75 are all dependent from claim 49 and as stated above, are drawn a method of determining the presence of a target analyte in a sample through the use of subpopulations of microspheres randomly distributed on a surface, wherein at least one subpopulation does not contain an optical signature and the use of fiducials to register images of the random array, wherein a first edge of said array is a fiducial edge (claim 64); wherein at least one of said fiducial fibers has a different shape from the others (claim 70); and wherein at least one of said fiducial microspheres does not comprise a label (claim 75).

Applicants respectfully submit, for the reasons set forth above, that Walt et al., Brenner et al., and Morris do not teach or suggest all of the elements of the methods claimed in claims 64, 70 and 75. More specifically, the combination of references does not teach or suggest the methods including the steps of "using said fiducial to register said first [second] data image to create a registered first [second] data image" and "comparing said first and second registered data images to determine the presence or absence of said target analyte." Applicants further submit that, for the reasons set forth below, Augenlicht et al. does not cure the deficiencies of Walt et al., Brenner et al., and Morris.

Augenlicht et al. is directed to detecting the expression of cloned genes by immobilizing nucleic acid from individual clones arranged in a pattern on a substrate such as nitrocellulose and

hybridizing nucleic acid probes to the immobilized nucleic acid with subsequent determination of the level of expression of individual genes in a sample. Augenlicht et al. teaches the use of fiducial markings to locate the position of the individual clones.

Furthermore, even if all of the elements of the claims were taught or suggested in the cited references, Applicants submit that one skilled in the art would not have been motivated to combine the references. The Examiner states that it would have been obvious to one of ordinary skill in the art to modify the substrate of Walt et al. or to modify the fiducial–containing array of Walt et al. by encompassing a fiducial of different shape for the expected benefit of rapid and accurate target analysis as suggested by Augenlicht (claims 64 and 70), (column 8, 15-29), or to modify the different sized fiducials of Walt et al. providing unlabeled fiducials of different size (claim 75) for the obvious benefit of convenience and economy of time and labor. Applicants respectfully traverse.

Initially, Applicants note that there is no teaching or suggestion in the cited references that would have motivated one of ordinary skill in the art to modify the references or combine reference teachings. The Examiner cites to the alleged obvious benefits of convenience and economy of time and labor and the expected benefit of rapid and accurate target analysis as the motivation to combine references to reach the claims of the present invention. However, obviousness is tested by what the combined teachings of the references would have suggested to those of ordinary skill in the art. It cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. And teachings of references can be combined *only* if there is some suggestion or incentive to do so. *In reFine, 5* USPQ2d *1596, 1599* (CAFC 1988) (quoting *In re Keller,* 208

USPQ 871,881 (CCPA 1981) *and ACS Hosp. Sys. v. Mont efiore Hosp.,* 221 USPQ 929, 933 (CAFC 1984)). Here, there is no such teaching.

Instead, Applicants note that Walt is directed to methods that utilize random arrays of microspheres dispersed on a substrate. The challenge encountered with such a random array was to establish a method of aligning multiple images of the same array so that the array could be decoded and the signal that resulted from binding of a target analyte could be correlated with a particular microsphere. In contrast, Augenlicht is directed to ordered arrays. That is, the location of each array element is known because the elements are placed at a particular location following the replica plating. Thus, at the time the invention was made, one of ordinary skill in the art would not have been motivated to combine the teachings of Augenlicht to solve the challenge of Walt. Augenlicht was concerned with different challenges than those faced by Walt.

Moreover, Applicants respectfully submit that one of ordinary skill in the art would not have had a reasonable expectation of success in practicing the invention as claimed based on the teachings of the cited references. Applicants note that Walt describes the use of arrays of microspheres distributed on substrates. The substrates can be planar and also can include fiber optic bundles. It is unclear where or how the fiducials, if any, are used in the method disclosed in Walt. Moreover, given the small size of the array of Walt it is unclear whether there would be adequate room around the periphery of the array for a fiducial similar to that disclosed in Augenlicht. Thus, it is unclear based on the teachings of the cited references how to make or prepare an array according to Walt with a fiducial according to Augenlicht because it is unclear from reading Augenlicht how the triangular fiducials are placed on the array of Augenlicht, much less how such triangular markings could be applied to an array as disclosed in Walt et al.

To this end, Applicants remind the Examiner that "[r]eferences relied on to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., they must place the claimed invention in the possession of the public." In re Payne, 203 USPQ 245, 255 (CCPA 1979). Here, Applicants submit that the Augenlicht fails to enable one of ordinary skill in the art how to prepare an array as taught in Walt with the fiducial as disclosed in Augenlicht. Accordingly, Applicants submit that the rejection is in error. Applicants respectfully request the Examiner to withdraw the rejection.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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